Guidance for Industry

Levothyroxine Sodium

Draft Guidance

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For questions on the content of the draft document contact Christine F. Rogers, 301-594-2041.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

On August 14, 1997, FDA announced in the *Federal Register* (62 FR 43535) that orally administered levothyroxine sodium drug products are new drugs. The notice stated that manufacturers who wish to continue to market these products must submit applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR part 314.

The notice stated that FDA is prepared to accept new drug applications (NDAs) for these products, including section 505(b)(2) applications.[2] An applicant making a submission under section 505(b)(2) of the Act may rely on investigations described in section 505(b)(1)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. A number of questions have arisen with respect to applications for levothyroxine sodium products. This guidance is intended to answer these questions.

II. REGULATORY QUESTIONS AND ANSWERS

A. Status of Marketed Products

Q: After August 14, 1997, is it permissible to begin marketing an unapproved levothyroxine sodium product that has never before been marketed?

A: No. As stated in the *Federal Register* notice, any levothyroxine sodium product marketed *for the first time* after August 14, 1997, must have an approved new drug application. Any product marketed without an approved application is an unapproved new drug and subject to enforcement action.

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[1] This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products and the Regulatory Policy Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on issues concerning applications for levothyroxine sodium. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] The notice also stated that a bioavailability study must be completed and submitted as part of a new drug application, including a 505(b)(2) application. On June 10, 1999, FDA published in the *Federal Register* a notice of availability of a draft guidance for industry entitled *In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets* to assist sponsors in conducting the bioavailability study.

Q: On August 14, 2000, what will be the status of a marketed product if an application for that product was submitted prior to August 14, 2000, but is not yet approved as of that date?

A: *Any* levothyroxine sodium product marketed on or after August 14, 2000, without an approved NDA will continue to be considered an unapproved new drug and will be subject to enforcement action (62 FR 43535, August 14, 1997). This will be the case even if an application for the product is undergoing review. Whether FDA will initiate enforcement action to remove an unapproved product from the market will depend upon its enforcement priorities and resources.

B. Cutoff Date for 505(b)(2) Applications

Q: Will FDA approve only one NDA and convert other 505(b)(2) applications to ANDAs?

A: No. It is possible that more than one NDA will be approved. FDA will not convert any filed NDA to an ANDA.

Q: Will there be a cutoff date after which FDA will no longer accept and review 505(b)(2) applications?

A. FDA will review all 505(b)(2) applications for levothyroxine sodium products filed before the first NDA for levothyroxine sodium products is approved. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA. If an application is refused for filing, it may be resubmitted as an ANDA, provided it meets the requirements of section 505(j) of the Act.

Q: What will happen to a 505(b)(2) application that has been filed, but not yet approved, when the first NDA for levothyroxine sodium is approved? What if the application was submitted, but not filed, when the first NDA is approved?

A: FDA will review all NDAs, including 505(b)(2) applications for duplicates, that have been filed even if an NDA is approved before review of an application has been completed. The FDA may refuse to file and review a 505(b)(2) application that was submitted, but not filed, before the first NDA for levothyroxine sodium is approved.

C. Requirements for 505(b)(2) Applications

Q: Should a 505(b)(2) application contain a patent certification?

A: All 505(b)(2) applications are subject to the patent certification requirements at 21 CFR 314.50(i). However, if there is no listed drug for levothyroxine sodium at the time the application is filed, the applicant need not make a patent certification.

After an NDA is approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the approved product (21 CFR 314.50(i)). If there are no patents listed for the approved product, the applicant should submit a statement, as described at 314.50(i)(1)(ii), that there are no relevant patents.

Q: Will a 505(b)(2) application for levothyroxine sodium be assessed a user fee? If so, is it a full fee or half fee?

A: Yes, a user fee will be assessed. The Act provides that a 505(b)(2) application is subject to an application fee if it requests approval of either (1) a molecular entity that is an active ingredient (including any salt or ester of an active ingredient) that has not been approved under section 505(b) of the Act, or (2) an indication for a use that has not been approved under section 505(b) of the Act (sections 735(1)(B) and 736(a)(1)(A)(i) of the Act). Levothyroxine sodium has been approved previously as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). However, levothyroxine sodium as a single-agent therapy has not been approved for any indication. Therefore, the FDA believes that single-agent therapy for thyroid-related disorders is a new indication for use. Therefore, applicants submitting 505(b)(2) applications for levothyroxine sodium must pay a user fee. But once an application has been approved, another 505(b)(2) application for levothyroxine sodium would not be subject to a fee unless the applicant seeks approval of an indication different from that approved in earlier applications.

A full fee would be assessed because clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval (section 736(a)(1)(A)(i) of the Act). These clinical data are expected to be in the form of literature reports, but are still considered to be clinical data for purposes of assessing user fees.

An applicant submitting a 505(b)(2) application for levothyroxine sodium may be eligible for a waiver or reduction of user fees under section 736(d) of the Act. For information on how to apply for a waiver, you may contact the Regulatory Policy Staff, CDER, HFD-7, 5600 Fishers Lane, Rockville, Maryland 20857, 301-594-2041.

Q: Are pediatric studies necessary?

A: As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred. Studies that are deferred are not required to be submitted until at least December 2, 2000.[3] Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the division the need for a pediatric assessment for the levothyroxine product proposed in an NDA. It is

[3] Please refer to 21 CFR 314.55 and the preamble to the final rule (63 FR 66632, December 2, 1998) for a discussion of the grounds for waiver or deferral of the pediatric study requirement.

possible that adequate data to support safety and effectiveness for pediatric use may be available in the scientific literature.

D. Exclusivity

Q: Will there be exclusivity for the first levothyroxine sodium product to be approved?

A: Exclusivity determinations are made at the time a drug product is approved. Although FDA cannot at this time be specific as to which, if any, applications may receive exclusivity, sponsors should consider some issues regarding the requirements for exclusivity. Five-year exclusivity is available for new chemical entities, which are drugs that contain no previously approved active moiety. Levothyroxine sodium has previously been approved as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). Three-year exclusivity is available for applications that contain reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.

E. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

Q: If the Agency approves multiple 505(b)(2) applications, how will they be rated in the Orange Book

A: They will be listed as BX — drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant must submit data comparing its product to a listed drug (*Approved Drug Products with Therapeutic Equivalence Evaluations* -- The Orange Book).

Q: Will FDA review a bioequivalence study submitted with an NDA that compares the product to an approved levothyroxine sodium product?

A: Yes. An NDA applicant may submit a bioequivalence study comparing its levothyroxine sodium product to one previously approved. If the products are bioequivalent, they will be AB-rated to each other.

F. ANDAs for Levothyroxine Sodium Products

Q: When will FDA choose a reference listed drug?

A: FDA chooses a reference listed drug when a manufacturer makes a request to submit an ANDA for a product that is eligible for approval under section 505(j) of the Act.

Q: How will FDA choose a reference listed drug for levothyroxine sodium tablets?

A: If there is only one approved product, that product will become the reference listed drug. If more than one product has been approved before FDA receives a request to submit an ANDA, the market leader among the approved products will be designated as the reference listed drug. FDA may also designate an additional reference listed drug if requested to do so by an ANDA sponsor.

Q: Will there be more than one reference listed drug?

A: It is possible.

III. SCIENTIFIC QUESTIONS AND ANSWERS

A. Stability Data

Q: How much stability data is required for an application to be acceptable for filing?

A: ICH and FDA stability guidances recommend 12 months' long-term data and 6 months' accelerated data at the time of NDA submission if a 24-month expiration date is requested. However, for levothyroxine sodium products to meet the compliance date specified in the August 14, 1997, *Federal Register* notice, 6 months' long-term data and 3 months' accelerated data will be sufficient. Additional stability data may be submitted as an amendment during the review process, and an expiration date will be granted based on the data submitted.

B. Dissolution Test

Q: The USP proposed a new dissolution test for levothyroxine sodium in the January-February 1999 *Pharmacopeial Forum*. Should NDA applicants use that proposed test or continue to use the current official method?

A: The proposed new dissolution test has not been adopted. Applicants should use the current official USP test. If the USP changes the official test after an NDA is submitted, an applicant can submit new data using that test as a phase-4 study.

C. Overage

Q: May a stability overage be used?

A: No.

Q: May a manufacturing overage be used?

A. Yes. The FDA permits the use of a manufacturing overage only in the unusual case when the product is manufactured to be 100 percent potent at the time of release and when the manufacturer can specifically document where in the manufacturing process the loss of potency occurs.